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NEUROLOGICAL EFFECTS OF CELIAC DISEASE

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Abstract

Celiac disease or gluten sensitivity may initially present as one or more neurological signs and/or symptoms. On the other hand, it may be associated with or complicated by neurological manifestations. Neurological presentations are rare in children but as many as 36% of adult patients present with neurological changes. With severe malnutrition after progression of celiac disease, different vitamin deficiencies may develop. Such problems can in turn overlap with previous neurological abnormalities including ataxia, epilepsy, neuropathy, dementia, and cognitive disorders. In this study, we aimed to review the neurological aspects of celiac disease. Early diagnosis and treatment could prevent related disability in patients with celiac disease.

Introduction

Celiac disease, also called gluten-sensitive enteropathy or nontropical sprue, is a common cause of malabsorption.(1) Allergic response to the cereal grain protein (gluten) causes small intestine inflammation and results in malabsorption. (1) In fact, celiac disease is an autoimmune inflammatory condition that affects small intestine. Reports in 1950s suggested the prevalence of celiac disease in Europe to range from 1 in 8000 to 1 in 4000 people. (1) However, new investigations based on small intestine biopsy have shown higher prevalence of 1 in 500 to 1 in 300 people in most countries. (1) The prevalence of celiac disease in the United States is as high as 1 in 113 people. (1)(3) Although celiac disease is classically a disorder among children, it has also been reported among

40-50 year-old individuals. In addition, women are affected twice more than men.(2)

The etiology of celiac disease is not clearly known. Many factors, such as environmental, genetic, and immunologic factors, are involved in the pathology of celiac disease. Gliadin, a part of gluten present in rye, wheat, and barley, is an environmental factor associated with celiac disease.(1) The immunologic component in the pathogenesis of celiac disease involves both innate and adaptive responses. The most important genes associated with susceptibility to celiac disease are human leukocyte antigen (HLA)-DQ2 and HLA-DQ8.(3)(4) Absence of this relationship fundamentally excludes the diagnosis of celiac disease. (1) HLA typing for both DQ2 and DQ8 may be useful in patients with equivocal small intestine biopsy. (5)(6) Serum antibodies [anti-gliadin immunoglobulin A (IgA) antibody, IgA anti-endomysial antibody, and IgA antibodies to tissue transglutaminase (tTG)] are present in celiac disease. Due to high specificity (90-95%) and high sensitivity (90-95%), antibody studies are frequently used to identify patients with celiac disease. (1)(7)

As for the Clinical Manifestation of Celiac disease. Few patients present with classical signs and symptoms primarily to celiac disease or secondary to vitamin deficiencies and nutrient malabsorption. A bigger group of individuals have some manifestations that are not related to gastrointestinal malabsorption, e.g. osteopenia, anemia, and neurologic complications. This type of disease is called atypical celiac disease. Most patients are asymptomatic and diagnosed by serologic investigation and histopathological studies. This type of disease is referred to as silent celiac disease. (1)

Although gluten-sensitivity is classically a disease of infants, celiac disease often presents in later, especially in the second and fifth, decades

of life.(8) Consequently, well-known features of a child with life threatening malabsorption is replaced by an atypical or silent celiac disease in adults.(8) Patients may experience typical gastroenterological manifestations such as steatorrhea, flatulence, bulky stool, and weight loss or complications of severe malnutrition such as anemia and metabolic disorder. They may also have atypical manifestations without gastrointestinal symptoms that present with folate or iron deficiency. (9) Therefore, asymptomatic relatives of patients with celiac disease have to be screened by serologic or small bowel biopsy studies.(1) On the other hand, there has been a shift from fewer patients who present with typical gastroenterological manifestations to more patients with silent or atypical disease. (9) Neurological presentations are rare in children but as many as 36% of adult patients present with neurological changes. (2)

Neurological effects

1- Cerebellar ataxia

Cerebellar ataxia (CA) is one of the most frequent neurological manifestations related to celiac disease (CD) (8), and may be the only and initial clinical manifestation of this disease (9) without any association with gastro-intestinal symptoms or malabsorption signs.Gluten ataxia is purely cerebellar and involves the entire cerebellum (10) , and it's clinical signs are :gait ataxia , limb ataxia,Dysarthria , pyramidal signs, altered eyes motions , progressive impairment of stability and erect position (11) and Rarely, CA is associated with myoclonus, palatal tremor, chorea and opsoclonus (12). Cerebellar ataxia have variant degrees of severity, The severity of CA is assessed at presentation with a simple clinical rating scale as:**mild**, when the patient is able to walk unaided. **moderate**, when

the patient needs walking aids/support to be able to walk or **Severe**, when the patient is wheelchair bound (13).

There are several theories for The diagnosis of gluten ataxia for example according to **lbara et al** , gluten ataxia may be diagnosed if the following conditions are present, positivity of IgA AGA and/or IgG AGA, presence of sporadic CA, duodenal histology compatible with CD, clinical response to gluten free diet (GFD). Anti-transglutaminase antibodies (TGA) IgG, such as TG2 and TG6, are often evident in this group of patients and are correlated to an immune response in the central nervous system (CNS) (14). Antibodies to TG2 and TG6 may be present in patients with ataxia and blood negative AGA (15). Gluten ataxia has a late mean age of clinical presentation, on average 53 years (range 13 to 90) (15) with a diagnostic delay of 10 years when compared to patients presenting with gastro-intestinal symptoms (mean age 43.8 +/- 15 years) (14). While **Hadjivassiliou et al**. (14) reported a prevalence of 78% of Blood IgG AGA, 65% IgA AGA, and 43% with both antibodies IgG and IgA. At present, however, the availability of TG6 antibodies analysis/testing is limited because these antibodies had only been discovered recently (2006) (14) and their importance in neurological manifestations of CD had not been established until 2008 (14). The role of autoimmunity in CD is well established due to the presence of a recognized target auto-antigen in the form of TG2 (13). The patients effected by gluten CA showed an immunological response against a primarily brain expressed TG, such as TG6 (16). Immunoglobulin deposits against TG6 and TG2 in the brain vessel walls could be found in patients with gluten ataxia (17). At this point, the time when Transglutaminase (TG) antibodies such as TG2, TG3, and TG6, appear in the blood stream, is not noted (14). Magnetic resonance (MR)

spectroscopic studies may show evidence of abnormal cerebellar neuronal physiology (18). A significant difference in mean

N-acetylaspartate/creatine levels has been observed between patients with gliadin antibodies and healthy controls (18).

2- Neuropathy

Another neurological manifestation of celiac disease is peripheral neuropathy. Some studies have reported that up to 50% of patients with celiac disease may develop a form of peripheral neuropathy.[19] Subclinical peripheral neuropathy in celiac patients without electrophysiological changes is demonstrated by lower pain threshold and reduced heat and touch sensations..[20] ,Normal nerve conduction while there are permanent and severe pain and sensory loss are evidences for small-fiber involvement and could be considered as early findings in celiac neuropathy, also Presence of many symptoms in favor of peripheral neuropathy while results of electro-diagnostic studies are normal, show peripheral neuropathy is restricted to small neurologic fiber alone in which electro-diagnostic study is not sensitive enough to detect abnormalities of small fiber.[21]

while in physical examination, The predominant manifestation of peripheral neuropathy is sensory neuropathy with variable involvement of large and small fibers.[21] Since peripheral neuropathy may precede the diagnosis of biopsy-proven celiac disease, celiac disease should be considered especially in patients with symmetrical distal form of sensory neuropathy.[22, 23] Another neuropathic manifestation of celiac disease is a rapidly progressing syndrome like : acute inflammatory demyelinating, polyneuropathy,mononeuritis multiplex, pure motor neuropathy,

autonomic dysfunction, Guillain-Barre-like syndrome.[23]A rare manifestation of neuropathy is associated with lymphoma in complicated and prolonged celiac disease. It may occur directly or indirectly as a paraneoplastic involvement.[24]Electrodiagnostic studies and biopsy samples from skin or sural nerve may be abnormal and autoantibodies against gangliosides may be detected.[25, 26]

3- Seizures

A specific seizure disorder syndrome has been recorded in celiac disease with bilateral occipital calcification. This intriguing, but rare entity was first described in 1970 and was later confirmed, particularly in reports from Italy. The majority of patients had complex partial seizures referable to the occipital or temporal lobes; however, generalized seizures may also occur. Calcification is generally bilateral and, pathologically, the calcifications consist of patchy pialangiomas, fibrosed veins and large microcalcifications containing calcium and silica (24, 25).

4-Headache

An association between celiac disease and migraine headaches was not established when compared to general population. However, results of functional imaging studies such as single photon emission computed tomography (SPECT) were in favor of migraine, and a gluten free diet may lead to a improvement in the migraine in these patients.[27]

4- Cognitive Complications of Celiac Disease

adult celiac patients often present with mild cognitive symptoms known as “brain fog” [28]. The most common features reported include :attention and concentration difficulties, word-retrieval challenges, episodic memory deficiency, disorientation or confusion episodes, declined mental acuity, various forms of dementia, including vascular dementia (VaD), Alzheimer’s disease (AD) and frontotemporal dementia, have been shown to be associated with CD [29,30] . so attention, memory, executive functions, and visuospatial abilities need to be screened among every patient with CD, both during the disease progression and at the time of diagnosis. Because direct link is yet to be known but A number of mechanisms have been put forward to account for the deleterious effect of gluten-associated diseases on cognitive abilities, including nutritional deficiencies, regional cerebral hypoperfusion, increased levels of circulating cytokines caused by systemic inflammation, and low levels of brain serotonin [31,32,33]. In general, however, limited research has dealt with this topic extensively. It is already known that AGA tends to react with the brain blood vessels [34], thus contributing to the findings from an extensive epidemiological investigation showing that CD results in an increased risk of dementia [35]. Additionally, CD displays a cross-reactivity with the neuronal synapsin 1 that regulates the release of neurotransmitters, suggesting that the antibody has the potential to disrupt the functions of the brain outside its vasculature [36]. At the same time, studies have associated AGA with increased depression rates among patients with and without the disease [37,38]. Therefore, there is a strong evidence to suggest that AGA positivity results in brain pathology, either by a proinflammatory state induction or by cross-reactivity phenomena. In addition, it is known that

anti-tTG6 antibodies are frequently the pathogenic trigger for neurological manifestations in CD [39,40].

As for treatment, cognitive and mood improvement was shown to occur only after a long-term GFD (>5 years) [28,41,42], indicating the rationale of prolonged gluten restriction on extra-intestinal symptoms of CD as well. Consequently, GFD should be administered as early as possible after the disease onset, given its potential neuroprotective effect. Undeniably, indeed, AGA levels tend to decrease when individuals take less gluten [43] and GFD has the potential to stop the development of other gluten-associated pathologies [39,44,45,46]. Nonetheless, the effect of GFD still remains a debatable issue and patients >65 years old present with worse cognitive performance compared to sex-and age-matched controls even after a long-term treatment with GFD [47].

6- Myoclonic Syndrome

A myoclonic syndrome, often accompanied by ataxia, may occur in celiac disease. This situation occurs in presence of normal levels of vitamins E and B12.[48] These patients have gastrointestinal symptoms such as abdominal pain, chronic diarrhea in different degrees, and action or reflex myoclonus.[49] Myoclonus may present as focal, multifocal, or generalized convulsions. It starts with polyspike discharges on electroencephalogram (EEG). Jerky movements will develop after discharges. In addition, opsoclonus-myoclonus has been described in a child with celiac disease.[50]

7 -Vitamin Deficiency Syndromes

Vitamin deficiency secondary to malabsorption in celiac disease can cause abnormal neurological findings.[51] For the presence of neurologic manifestations secondary to celiac disease, severe and extensive involvement of small intestine, especially its proximal part, is necessary.[51]

-Thiamin (vitamin B1) deficiency due to celiac disease per se is rare but was reported in the presence of concomitant alcohol abuse or substance dependence.[51] **Wernicke-Korsakoff syndrome** results in thiamin deficiency. In addition, anything that encourages glucose metabolism will exacerbate an existing clinical or sub-clinical thiamine deficiency. [52] On the other hand, thiamine deficiency may lead to beriberi which in turn leads to a sensory axonal neuropathy and may be presented by burning feet and cardiac failure.[53] alsoThe main absorptive site for vitamin B12 is the distal part of the small intestine. Since this site is not usually involved in celiac disease, vitamin B12 deficiency is generally uncommon in uncomplicated celiac disease. However, vitamin B12 deficiency has been reported in celiac patients due to pancreatic involvement and bacterial overgrowth that had altered ileal receptors uptake and motility function of the small bowel. Another possible reason for vitamin B12 deficiency is the presence of autoimmune gastritis with pernicious anemia accompanied by celiac disease.[54] whileVitamin E deficiency can lead to ataxia and sensory neuropathy in patients with celiac disease.[55] Niacin deficiency may present by dementia, ataxia, and seizure but this problem is rare.[56]

Conclusion

In the end of this study we found that celiac disease in addition to its gastrointestinal manifestations it also has several effects on the nervous system that appear in a variant degree between patients , with cerebral ataxia being the most common effect , CA has many signs as it involves the whole cerebellum. In addition to cerebral ataxia , peripheral neuropathy may also occur and it mainly involves the small fibers and mostly manifest as sensory loss and sever pain. We also found that celiac disease may cause seizures, the majority of these seizures being complex partial seizure, and less frequently generalized seizures may occur. Celiac disease also associated with concentration difficulties, episodic memory deficiency and other cognitive complications that are found to be improved after committing to a long term gluten free diet. Another important finding in this study is the neurological problems that occur secondary to vitamin deficiency that results from the malabsorption that is associated with celiac disease. As for the treatment of these complications many of them are found to be improving with diet control but further studies are needed to determine the role of gluten-free diets in treatment of neurological manifestations in the absence of overt intestinal disease. Nutritional deficiencies, which are rarely the sole cause of neurological manifestations, are easily correctable

Refrences

1. Binder HJ. Disorder of absorption. In: Fauci AS, Eugene B, Hauser SL, editors. *Harrison's principles of internal medicine.* 17th ed. New York, NY: McGraw Hill; 2008. pp. 2460–76. [Google Scholar]
2. Chaudhry V, Ravich WJ. *Neurology and General Medicine.* 3th ed. New York, NY: Churchill Livingstone; 2001. Other neurological disorders associated with gastrointestinal, liver, or pancreatic diseases; pp. 283–4. [Google Scholar]
3. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med.* 2003;163(3):286–92. [PubMed] [Google Scholar]
4. Maki M, Mustalahti K, Kokkonen J, et al. Prevalence of Celiac disease among children in Finland. *N Engl J Med.* 2003;348(25):2517–24. [PubMed] [Google Scholar]
5. Collin P, Reunala T, Rasmussen M, et al. High incidence and prevalence of adult coeliac disease. Augmented diagnostic approach. *Scand J Gastroenterol.* 1997;32(11):1129–33. [PubMed] [Google Scholar]
6. Murray JA, Van DC, Plevak MF, et al. Trends in the identification and clinical features of celiac disease in a North American community, 1950-2001. *ClinGastroenterolHepatol.* 2003;1(1):19–27. [PubMed] [Google Scholar]
7. Fasano A. Celiac disease--how to handle a clinical chameleon. *N Engl J Med.* 2003;348(25):2568–70. [PubMed] [Google Scholar]
8. Fasano A. Celiac disease--how to handle a clinical chameleon. N Engl J Med. 2003; 348(25) : 2568 -70 [DOI][PubMed
9. Hadjivassiliou M, Gibson A, Davies-Jones GA, Lobo AJ, Stephenson TJ, Milford-Ward A. Does cryptic gluten sensitivity play a part in neurological illness? Lancet. 1996; 347(8998) : 369 -71 [PubMed]
10. Khwaja GA, Bohra V, Duggal A, Ghuge VV, Chaudhary N. Gluten Sensitivity - A Potentially Reversible Cause of Progressive Cerebellar Ataxia and Myoclonus - A Case Report. J ClinDiagn Res. 2015; 9(11) : OD07 -8 [DOI][PubMed]
11. Hadjivassiliou M, Aeschlimann P, Strigun A, Sanders DS, Woodroofe N, Aeschlimann D. Autoantibodies in gluten ataxia recognize a novel neuronal transglutaminase. Ann Neurol. 2008; 64(3) : 332 -43 [DOI][PubMed]
12. Hadjivassiliou M. Ataxia Disorders 1 Clinical Neurological Series 3. 2011
13. Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, Davies-Jones GA, Gibson A, Jarratt JA, et al. Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet. 1998; 352(9140) : 1582 -5 [PubMed]
14. Hadjivassiliou M, Rao DG, Grinewald RA, Aeschlimann DP, Sarrigiannis PG, Hoggard N, et al. Neurological Dysfunction in Coeliac Disease and Non-Coeliac Gluten Sensitivity. Am J Gastroenterol. 2016; 111(4) : 561 -7 [DOI][PubMed]
15. Hadjivassiliou M, Boscolo S, Tongiorgi E, Grunewald RA, Sharrack B, Sanders DS, et al. Cerebellar ataxia as a possible organ-specific autoimmune disease. MovDisord. 2008; 23(10) : 1370 -7 [DOI][PubMed]
16. Hadjivassiliou M, Aeschlimann P, Sanders DS, Maki M, Kaukinen K, Grunewald RA, et al. Transglutaminase 6 antibodies in the diagnosis of gluten ataxia. Neurology. 2013; 80(19) : 1740 -5 [DOI][PubMed]

17. Hadjivassiliou M, Maki M, Sanders DS, Williamson CA, Grunewald RA, Woodroofe NM, et al. Autoantibody targeting of brain and intestinal transglutaminase in gluten ataxia. Neurology. 2006; 66(3) : 373 -7 [DOI][PubMed]
18. Wilkinson ID, Hadjivassiliou M, Dickson JM, Wallis L, Grunewald RA, Coley SC, et al. Cerebellar abnormalities on proton MR spectroscopy in gluten ataxia. J NeurolNeurosurg Psychiatry. 2005; 76(7) : 1011 -3 [DOI][PubMed]
19. Cicarelli G, Della RG, Amboni M, et al. Clinical and neurological abnormalities in adult celiac disease. Neurol Sci. 2003;24(5):311–7. [PubMed] [Google Scholar]
20. Chin RL, Latov N, Green PH, et al. Neurologic complications of celiac disease. J ClinNeuromuscul Dis. 2004;5(3):129–37. [PubMed] [Google Scholar]
21. Sander HW, Chin RL, Brannagan TH, et al. Should neuropathy patients be screened for celiac disease? Neurology. 2003;60:1566–8. [Google Scholar]
22. Freeman HJ. Neurological disorders in adult celiac disease. Can J Gastroenterol. 2008;22(11):909–11. [PMC free article] [PubMed] [Google Scholar]
23. Chin RL, Sander HW, Brannagan TH, et al. Celiac neuropathy. Neurology. 2003;60(10):1581–5. [PubMed] [Google Scholar]
24. Ascaso FJ, Torres M, Bergua JM, et al. Progressive external ophthalmoplegia: a paraneoplastic manifestation of lymphoma. Eur J Ophthalmol. 2002;12(4):315–8. [PubMed] [Google Scholar]
25. .Brannagan TH, 3rd, Hays AP, Chin SS, et al. Small-fiber neuropathy/neuronopathy associated with celiac disease: skin biopsy findings. Arch Neurol. 2005;62(10):1574–8. [PubMed] [Google Scholar]
26. .Gobbi G, Bouquet F, Greco L, et al. Coeliac disease, epilepsy, and cerebral calcifications. The Italian Working Group on Coeliac Disease and Epilepsy. Lancet. 1992;340(8817):439–43. [PubMed] [Google Scholar]
27. .Gabrielli M, Cremonini F, Fiore G, et al. Association between migraine and Celiac disease: results from a preliminary case-control and therapeutic study. Am J Gastroenterol. 2003;98(3):625–9. [PubMed] [Google Scholar]
28. Yelland G.W. Gluten-induced cognitive impairment (“brain fog”) in coeliac disease. J. Gastroenterol. Hepatol. 2017;32:90–93. doi: 10.1111/jgh.13706. [PubMed] [CrossRef] [Google Scholar]
29. Lurie Y., Landau D.A., Pfeffer J., Oren R. Celiac disease diagnosed in the elderly. J. Clin. Gastroenterol. 2008;42:59–61. doi: 10.1097/01.mcg.0000247995.12087.7b. [PubMed] [CrossRef] [Google Scholar]
30. Makhlouf S., Messelmani M., Zaouali J., Mrissa R. Cognitive impairment in celiac disease and non-celiac gluten sensitivity: Review of literature on the main cognitive impairments, the imaging and the effect of gluten free diet. Acta Neurol. Belg. 2018;118:21–27. doi: 10.1007/s13760-017-0870-z. [PubMed] [CrossRef] [Google Scholar]
31. . Briani C., Zara G., Alaedini A., Grassivaro F., Ruggero S., Toffanin E., Albergoni M.P., Luca M., Giometto B., Ermani M., et al. Neurological complications of celiac disease and autoimmune mechanisms: A prospective study. J. Neuroimmunol. 2008;195:171–175. doi: 10.1016/j.jneuroim.2008.01.008. [PubMed] [CrossRef] [Google Scholar]
32. Addolorato G., di Giuda D., de Rossi G., Valenza V., Domenicali M., Caputo F., Gasbarrini A., Capristo E., Gasbarrini G. Regional cerebral hypoperfusion in patients with celiac disease. Am. J. Med. 2004;116:312–317. doi: 10.1016/j.amjmed.2003.09.037. [PubMed] [CrossRef] [Google Scholar]

33. Della Nave R., Magaudda A., Michelucci R., Capizzi G., Calabrò A., Guerrini L., Gavazzi C., Diciotti S., Riguzzi P., Daniele O., et al. Whole-brain histogram and voxel-based analyses of apparent diffusion coefficient and magnetization transfer ratio in celiac disease, epilepsy, and cerebral calcifications syndrome. Am. J. Neuroradiol. 2007;28:479–485. [PMC free article] [PubMed] [Google Scholar]
34. Pratesi R., Gandolfi L., Friedman H., Farage L., de Castro C.A., Catassi C. Serum IgA antibodies from patients with coeliac disease react strongly with human brain blood-vessel structures. Scand. J. Gastroenterol. 1998;33:817–821. [PubMed] [Google Scholar]
35. . Lebwohl B., Luchsinger J.A., Freedberg D.E., Green P.H.R., Ludvigsson J.F. Risk of Dementia in Patients with Celiac Disease: A Population-Based Cohort Study. J. Alzheimer's Dis. 2016;49:179–185. doi: 10.3233/JAD-150388. [PubMed] [CrossRef] [Google Scholar]
36. Alaedini A., Okamoto H., Briani C., Wollenberg K., Shill H.A., Bushara K.O., Sander H.W., Green P.H., Hallett M., Latov N. Immune cross-reactivity in celiac disease: Anti-gliadin antibodies bind to neuronal synapsin I. J. Immunol. 2007;178:6590–6595. doi: 10.4049/jimmunol.178.10.6590. [PubMed] [CrossRef] [Google Scholar]
37. Ludvigsson J.F., Reutfors J., Ösby U., Ekbom A., Montgomery S.M. Coeliac disease and risk of mood disorders—A general population-based cohort study. J. Affect. Disord. 2007;99:117–126. doi: 10.1016/j.jad.2006.08.032. [PubMed] [CrossRef] [Google Scholar]
38. Ruuskanen A., Kaukinen K., Collin P., Huhtala H., Valve R., Mäki M., Luostarinen L. Positive serum antigliadin antibodies without celiac disease in the elderly population: Does it matter? Scand. J. Gastroenterol. 2010;45:1197–1202. doi: 10.3109/00365521.2010.496491. [PubMed] [CrossRef] [Google Scholar]
39. Hadjivassiliou M., Sanders D.S., Grünewald R.A., Woodroofe N., Boscolo S., Aeschlimann D. Gluten sensitivity: From gut to brain. Lancet Neurol. 2010;9:318–330. doi: 10.1016/S1474-4422(09)70290-X. [PubMed] [CrossRef] [Google Scholar]
40. Losurdo G., Principi M., Iannone A., Amoruso A., Ierardi E., di Leo A., Barone M. Extra-intestinal manifestations of non-celiac gluten sensitivity: An expanding paradigm. World J. Gastroenterol. 2018;24:1521–1530. doi: 10.3748/wjg.v24.i14.1521. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
41. Lichtwark I.T., Newnham E.D., Robinson S.R., Shepherd S.J., Hosking P., Gibson P.R., Yelland G.W. Cognitive impairment in coeliac disease improves on a gluten-free diet and correlates with histological and serological indices of disease severity. Aliment. Pharmacol. Ther. 2014;40:160–170. doi: 10.1111/apt.12809. [PubMed] [CrossRef] [Google Scholar]
42. . Van Hees N.J., Van der Does W., Giltay E.J. Coeliac disease, diet adherence and depressive symptoms. J. Psychosom. Res. 2013;74:155–160. doi: 10.1016/j.jpsychores.2012.11.007. [PubMed] [CrossRef] [Google Scholar]
43. Valletta E.A., Mastella G. Adherence to gluten-free diet and serum antigliadin antibodies in celiac disease. Digestion. 1990;47:20–23. doi: 10.1159/000200471. [PubMed] [CrossRef] [Google Scholar]
44. Hadjivassiliou M., Duker A.P., Sanders D.S. Gluten-related neurologic dysfunction. Handb. Clin. Neurol. 2014;120:607–619. doi: 10.1016/B978-0-7020-4087-0.00041-3. [PubMed] [CrossRef] [Google Scholar]
45. Caio G., Volta U., Tovoli F., de Giorgio R. Effect of gluten free diet on immune response to gliadin in patients with non-celiac gluten sensitivity. BMC Gastroenterol. 2014;14:26. doi: 10.1186/1471-230X-14-26. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

46. . Hadjivassiliou M., Grünewald R.A., Sanders D.S., Shanmugarajah P., Hoggard N. Effect of gluten-free diet on cerebellar MR spectroscopy in gluten ataxia. Neurology. 2017;89:705–709. doi: 10.1212/WNL.0000000000004237. [PubMed] [CrossRef] [Google Scholar]
47. Casella S., Zanini B., Lanzarotto F., Ricci C., Marengoni A., Romanelli G., Lanzini A. Cognitive performance is impaired in celiac patients on gluten free diet: A case-control study in patients older than 65 years of age. Dig. Liver Dis. 2012;44:729–735. doi: 10.1016/j.dld.2012.03.008. [PubMed] [CrossRef] [Google Scholar]
48. Hanagasi HA, Gurol E, Sahin HA, et al. Atypical neurological involvement associated with celiac disease. Eur J Neurol. 2001;8(1):67–9. [PubMed] [Google Scholar]
49. Lockman LA, Sung JH, Krivit W. Acute parkinsonian syndrome with demyelinating leukoencephalopathy in bone marrow transplant recipients. Pediatr Neurol. 1991;7(6):457–63. [PubMed] [Google Scholar]
50. Cooke WT. The neurological manifestations of malabsorption. Postgrad Med J. 1978;54(637):760–2. [PMC free article] [PubMed] [Google Scholar]
51. Robinson K. Wernicke's encephalopathy. Emerg Nurse. 2003;11(5):30–3. [PubMed] [Google Scholar]
52. Jeyakumar D. Beri-beri in immigrant workers--a report of three cases. Med J Malaysia. 1994;49(2):187–91. [PubMed] [Google Scholar]
53. Freeman HJ. Pancreatic endocrine and exocrine changes in celiac disease. World J Gastroenterol. 2007;13(47):6344–6. [PMC free article] [PubMed] [Google Scholar]
54. Hammans SR, Kennedy CR. Ataxia with isolated vitamin E deficiency presenting as mutation negative Friedreich's ataxia. J NeurolNeurosurg Psychiatry. 1998;64(3):368–70. [PMC free article] [PubMed] [Google Scholar]
55. Reuler JB, Girard DE, Cooney TG. Current concepts. Wernicke's encephalopathy. N Engl J Med. 1985;312(16):1035–9. [PubMed] [Google Scholar]
56. Swinson CM, Levi AJ. Is coeliac disease underdiagnosed? Br Med J. 1980;281(6250):1258–60. [PMC free article] [PubMed] [Google Scholar]